REMARKS/ARGUMENTS

Claims 1, 2, 6, 9, 10, 15, 16, and 23-32 have been rejected. Claims 2 and 16 have been cancelled and their limitations incorporated into their base claims. Claims 6, 9-10, 15, 23-26, 28 and 30 have been amended to correct dependencies in light of the cancellation of claims 2 and 16. Accordingly, no new matter has been introduced by way of these claim amendments.

Claims 1, 6, 9, 10, 15, and 23-32 are currently under examination in the application. Reexamination and reconsideration of the claims are respectfully requested in view of the following remarks. The Examiner's comments in the Office Action dated May 23, 2008 are addressed below in the order set forth therein.

The Objection to the Specification/Abstract Should Be Withdrawn

The Examiner has objected to the abstract and suggested amendments for clarity and conciseness. Applicants have amended the abstract as suggested. Accordingly, this objection has been obviated and Applicants request that it be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Claims 1 and 15 have been rejected for lack of enablement for the use of any *Trichilia* species within the claimed methods. However, the Examiner states that the specification is enabling with respect to *Trichilia catigua*. Without acceding to the propriety of the Examiner's rejection, in the interest of advancing prosecution Applicants have amended the claims to be directed to *Trichilia catigua* A. Juss. Accordingly, Applicants submit that this rejection has been obviated and request that it be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §103(a), Should Be Withdrawn

The Examiner has rejected claims 1, 2, 6, 9-10, 15, 16, and 23-32 for allegedly being obvious in view of the combination of Andre *et al.* (WO200296441), Sander *et al.* (US 6,335,039), and Kowey *et al.* (Cardiovascular Res. 17:106-112 (1982)). This rejection is

traversed for the reasons provided below.

Applicants call the Examiner's attention to the Declaration of Dr. Irineu Tadeu Velasco, filed concurrently herewith. References cited by Dr. Velasco that are not already of record are provided with the concurrently filed Information Disclosure Statement. Dr. Velasco is skilled in the art of the field of the invention, having received a Ph.D. in Physiology and Pharmacology at Biomedical Sciences, and a medical degree from Medical Sciences School of Santa Casa of São Paulo - FCMSCSP. He is currently a Professor of Clinical Medicine at the Medical School of the University of São Paulo (USP).

As described by Dr. Velasco, one of skill in the art would not have had a reasonable expectation of success in the use of *Trichilia catigua* for the combat or reversion of ventricular fibrillation on the basis of the art cited by the Examiner. For example, Dr. Velasco explains that the Kowey *et al.* study is restrained to a specific situation and is not representative of treatment in human patients. The mechanism of ventricular fibrillation involves very complex electrophysiologic alterations (see Weiss *et al.* (2004) *Ann. NY Academy of Sciences,* 1015:122-132). Thus, vasodilatation itself is not predictive of antifibrillatory action.

Applicants also submit that the Examiner's rejection on the basis of an "obvious to try" rationale is both a misapplication of the law and a misapplication of the USPTO's own examination guidelines. As previously argued by Applicants, the Federal Circuit has specified that the "obvious to try" standard requires an assessment of whether there are "a finite number of identified, predictable solutions" as well as a reasonable expectation of success in view of the predictability of the art. In *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.*, slip op. 2007-1223 (Fed. Cir. Mar. 31, 2008), the Federal Circuit held that the FBPase inhibitor topiramate and its use as an anticonvulsant were not obvious. In its decision, the Federal Circuit rejected the argument that because FBPase inhibitors were known to be useful to treat diabetes, one of skill in the art would have had a reason to design such inhibitors because of "a design need or market pressure to solve a problem" and because of "a finite number of identified, predictable solutions." *Id.*, slip op. at 9. In particular, the court found that there was significant evidence to show that the identification of topiramate "[did] not present a finite (and small in the

context of the art) number of options easily traversed to show obviousness." *Id.* The court pointed to the unpredictability of the art and the need to test topiramate to determine whether it demonstrated anticonvulsant properties, and rejected an approach to obviousness that "simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate was obvious." *Id.* at 10. Thus, the "obvious to try" standard requires a finding that there were a finite number of identified and predictable solutions as well as a reasonable expectation of success in view of the predictability of the art.

In addition to Federal Circuit case law, the USPTO's "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.*" (hereinafter "the Guidelines") require specific findings in the context of applying an "obvious to try" standard (72 *Fed. Reg.* 57526, 57532). In particular, the Guidelines state that:

> To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:
>
> (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
>
> (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
>
> (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
>
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Id. Accordingly, under the second and third elements, an Examiner must find that there were a finite number of identified and predictable solutions as well as a reasonable expectation of success in view of that predictability. The Guidelines go on to state that "[i]f any of these

findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." *Id.*

In the present case, there is no basis for a finding that there were a finite number of identified and predictable solutions or a reasonable expectation of success in view of the predictability of the art. As Applicants have previously argued, the present discovery that the claimed plant extracts were useful in the treatment of ventricular fibrillation did not represent a selection from a finite number of predictable solutions, but instead reflects the identification of the claimed plant extracts as having efficacy for a new use (ventricular fibrillation) in spite of the number, complexity, and unpredictability of the alternatives. This unpredictability is acknowledged by Kowey *et al.*, who state that although they observed protective effects of prostacyclin, prostaglandin E_1, and nitroglycerin on vulnerability to ventricular fibrillation, "[i]t remains to be determined whether other vasodilator drugs possess a similar potential for protection against malignant arrhythmia" (see Conclusion on page 111 of Kowey *et al.*).

The Examiner acknowledges that "[the term] vasodilator encompasses a wide range of structurally distinct compounds" (Page 10 of the Office Action of May 23, 2008). However, the Examiner proceeds to conclude that, "although some of the vasodilators may fail to show reduction in ventricular fibrillation as pointed out by Applicant, according to the teaching of the references, it is still obvious to try from among the known prior art vasodilators" (Page 10 of the Office Action of May 23, 2008). This conclusion ignores the fact that the wide structural range of the genus of vasodilators coupled with the lack of predictability regarding whether any individual member of that genus would be useful in reducing ventricular fibrillation does not support a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem.

The fact that there is unpredictability in the art is further highlighted by the evidence Applicants have described relating to the mechanism by which the claimed extracts exert their effects on ventricular fibrillation. Applicants argued that Pontieri *et al.* ((2007) *J. Electrocardiology* 40(6):534.e1-534.e8) showed that Catuama and *Trichilia Catigua* prolonged conduction time, Catuama prolonged phase 2 of the monophasic action potential (MAP), and

Ptychopetalum olacoides prolonged phase 3 of the MAP and that these results suggest specific actions of the claimed plant extracts on the membrane channels of the heart. Arrhythmia is caused by many reentrant electrical circuits acting through the ventricles, and the antiarrhythmic action of the claimed extracts occurs through their effect on ionic channels in the heart. Any antifibrillatory drug must have a strong action on the electrophysiologic properties of the heart, especially on ventricular repolarization. Although vasodilators can decrease sudden death in myocardial infarction (preventing ventricular remodeling and thus ventricular dysfunction), vasodilators are not used for prevention of sudden death in individuals at risk for the simple reason that their action is not enough to guarantee safety for the patient. If vasodilating action was enough, the millions of dollars spent annually with implantable automatic defibrillators could be saved. To conclude, there is not enough support in the scientific literature that antifibrillatory action is based on vasodilating properties, and the present data are based on the electrophysiological effects of the claimed extracts and not their vasodilating effects.

In response to Applicants previous arguments, the Examiner appears to rely on the statement by Pontieri *et al.* that "the mechanism of action of herbal extract Catauma still needs to be better investigated" for the Examiner's argument that "there is no evidence that the claimed herbal extracts exert ventricular fibrillation through mechanisms other than vasodilation, and there is no basis to conclude that the prolonged intraventricular condution [*sic*] and plateau duration of repolarization on MAP is not due to vasodilation" (See Page 11 of the Office Action of May 23, 2008). However, the fact that additional study is suggested by Pontieri *et al.* to further elucidate the mechanism of action does not support the Examiner's conclusion that the electrophysiological data they describe is invalid or nonexistent.

In summary, because there is no basis for a finding that there were a finite number of identified and predictable solutions or a reasonable expectation of success in view of the predictability of the art, a *prima facie* case of obviousness has not been established. Applicants therefore request that this rejection be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the objection to the specification and rejections of the claims under 35 U.S.C. §§112, First Paragraph, and 103(a) are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required. However, in the event that extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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ELECTRONICALLY FILED USING THE EFS-WEB ELECTRONIC FILING SYSTEM OF THE UNITED STATES PATENT & TRADEMARK OFFICE ON SEPTEMBER 22, 2008.